46. A blood analysis kit for performing a reverse ABO blood type comprising:

(a) a container having therein reagent red blood cells bearing group A antigen and reagent red blood cells bearing B antigen, wherein one of the populations of reagent red blood cells is stained;

(b) reaction means for carrying out the reverse ABO blood type; and

(c) instructions for performing the reverse ABO blood type.

47. The kit of claim 46 wherein the reaction means for performing the reverse ABO blood type is selected from the group consisting of tube, microplate, slide, slide platform and column agglutination technology.

48. The kit of claim 47 wherein the reaction means for carrying out the reverse ABO blood type is a column agglutination test reaction vessel.

49. The method of claim 16 wherein the sample of blood is serum or plasma.

50. The method of claim 25 wherein the sample of blood is serum or plasma.

51. The method of claim 31 wherein the sample of blood is serum or plasma.

REMARKS

Claims 16, 20, 22-23, and 25-28 are pending in the application and have been finally rejected. After entry of this Preliminary Amendment which entry is respectfully requested, claims 16, 20, 22-23, 25-28 and 29-51 will be in this case. It is respectfully submitted that the amended claims, as well as those newly added, are fully

supported in the specification as filed and that no new matter has been added.

The amendments have been made pursuant to the requirements of Rule 121 of the Rules of Practice. Specifically, the pending claims are written above in clean form and in accordance with 37 C.F.R. § 1.121(c)(1)(i) and § 1.121(c)(3). Pursuant to the requirements of 37 C.F.R.§ 1.121(c)(1)(ii), another version of the amended claims is attached hereto as Exhibit A. This Exhibit A version has been marked up to show all changes made in this amendment relative to the previous version of each claim. As stated hereinabove, the amendments do not constitute new matter. Entry and consideration of the amendments is therefore respectfully requested.

Informal Drawings

The Examiner has acknowledged Applicants' indication that the requirement for submission of formal drawings is being held in abeyance pending the indication of allowable subject matter.

Rejection under 35 U.S.C. §112 first paragraph

The specification was objected to and claims 16, 20, 22, 23 and 25-28 are rejected under 35 U.S.C. § 112, first paragraph, for reasons that the specification allegedly contains subject matter which was not described in such as way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner avers that as set forth, Applicant desires simultaneous determination of forward and reverse ABO

blood group yet provides no guidance for how one accomplishes such simultaneous determination with the separate combinations of anti-A antibodies and anti-B antibodies (forward), or of A-bearing cells and B-bearing cells (reverse). The Examiner has not found Applicants' reference to Example 2 Part C persuasive as the Examiner avers the Example is drawn only to reverse ABO blood grouping and not simultaneous determination of forward and reverse ABO blood group.

Applicants have amended claims 16, 20, 22-23, and 25-28 and have added new claims 29-51. Claims currently pending are directed to the following:
claims 16, 20, 22, 23, 29 and 49: a method of analyzing blood in a reverse test;
claims 25-28, 30 and 50: a method for determining reverse ABO blood type of two cell populations in a single test;
claims 31-35 and 51: a method of simultaneous testing for blood antibody using two cell populations;
claims 36-41: a method of performing an antibody screen in a single test;
claims 42-45: a blood analysis kit for performing antibody testing; and
claims 46-48: a blood analysis kit for performing a reverse ABO blood type.

The claims find support in the application as filed as follows:
claims 16, 20, 22, 23, 25-35 and 49-51: page 5 line 22- page 6 line 2; page 13, line 28- page 14 line 8; page 22 line 4 - page 24 line 21; Example 2; page 30 lines 1-17; page 31 lines 5-7; Table 6 (columns 5 and 6 therein); and Figure 6;

claims 36-48: all the above and in particular page 5 line 22 - page 6 line 2. Claims 36-45 to the antibody test find support

claims 42-48: all the above.

Claims 16, 20, 22, 23 and 25-28 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner avers that in claims 16, 20, 22, 23, and 25-28, the interrelationships of the sample or samples are not clear. The Examiner further states that Applicants have not addressed the lack of clarity as to the interrelationships of one or more sample(s) in the different steps. It is further averred that in claims 23 and 28, it is not clear how the computerized imaging system is related to or further limits "visual analysis" or if the imaging system is intended to limit "spectrophotometric analysis".

Regarding the Examiner's query concerning the interrelationships of the samples in claims 16, 20, 22, 23 and 25-28, Applicants have herein amended claims such that the Examiner's rejection has now been obviated. Regarding the Examiner's query as to how the computerized imaging system is related to or further limits "visual analysis" or if the imaging system is intended to limit "spectrophotometric analysis", Applicants have amended claims 23 and 28 to state the detection methods in the alternative. Applicants have deleted the reference to spectrophotometric analysis.

Rejection Under 35 USC 102(b)

Claims 1-11 and 14-20 were rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Ullman (U.S. Pat. No. 4,584,277) for reasons of record; the Examiner avers Ullman teaches fluorescently labeled anti-blood group antigen antibodies and fluorescently labeled erythrocytes having blood group antigens thereon added simultaneously or sequentially to a sample of whole blood for multiparameter analysis of ABO blood type and isoantibodies (i.e. reverse blood typing) (see e.g. col. 3-4). The Examiner avers that a variety of combinations of parameters and suitable reagents are taught (see e.g. col. 3, Table 1); that suitable fluorescent labels are taught (e.g. col. 8-9); and inherently, antibodies of the ABO system are generally IgM.

In addition, the Examiner notes that the recitation of column agglutination technology for visual analysis is in the alternative.

Applicants have amended pending claims and have added new claims. The amended and new claims now recite subjecting the admixture to visual *or* computerized imaging analysis. In all cases, the method is performed in a single test, which may be a tube, microplate, slide, slide platform and column agglutination technology. Preferably the analysis is performed using column agglutination technology. Nothing in Ullman teaches use of visual or automated computerized detection, the Ullman disclosure being directed to automated fluorescent detection. Claim 20, depending as it does on amended claim 16, and claiming that the reagent red blood cells are stained for said column agglutination technology, is

similarly neither taught nor suggested in Ullman. Applicants have deleted the reference to spectrophotometric analysis. For these reasons, Applicants respectfully submit that all the currently pending claims are patentable over Ullman.

Claims 16, 20, 22, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Yves [Lapierre] et al. (U.S. Pat. No. 5,338,689) for reasons of record; the Examiner avers that LaPierre et al. teaches a column agglutination assay and device for determination of agglutinated reactants, especially red blood cells in forward and reverse blood typing assays (see e.g. Figs. 5-7). The Examiner avers that the blood typing assays require the addition and reaction of reagents as instantly claimed (see e.g. col. 4-6), and that the reference teaches that the solid carrier particles, e.g. erythrocytes, can be naturally colored or can be stained or labeled (see e.g. col. 2).

Applicants traverse the rejection for the following reasons. Applicants respectfully submit that nothing in LaPierre teaches or suggests use of Applicants' methods of treating a population of reagent red blood cells with a dye in order to alter the color of one reagent cell population with respect to the other, and then using the two reagent cell populations simultaneously in one assay to determine reverse ABO blood group. In Applicants' methods is taught treatment of one population of reagent red blood cells with sodium azide or cyanide (thereby turning the red color to brown). After agglutination in accordance with the methods of the invention, the brown agglutinates are discriminated from the red agglutinates either visually or via automated computerized reader

thereby detecting the population of cells in a single test without the need to perform a confirmatory test. See specification at page 22 lines 4-14, and page 31 lines 5-17, Table 6 and Figure 6, wherein it is shown that agglutinated cells of one color (e.g., brown) are distinguishable from unagglutinated cells of another color (e.g., red).

Applicants therefore respectfully submit that since nothing in LaPierre teaches or suggests *discrimination of two distinct cell populations in a single test*, the instant claims are patentable thereover and the rejection should be withdrawn.

Claims 16, 20, 22 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Chachowski et al. (U.S. Pat. No. 5,552,064) for reasons of record; the Examiner avers Chachowski et al. teach a column agglutination assay and device (see e.g. col. 4-5) for determination of agglutinated reactants, especially red blood cells in forward and reverse blood typing assays (see e.g. col. 6-8). The Examiner further avers that inherently the blood typing assays require the addition and reaction of reagents as instantly claimed and that the reference teaches that erythrocytes are naturally stained by their hemoglobin content (see e.g. col. 7).

Applicants traverse this rejection in that nothing in Chachowski et al. teaches Applicants' methods of treating a population of reagent red blood cells with dye in order to alter the color of that one population with respect to the other. Applicants teach treatment of one population of reagent red blood cells with sodium azide or cyanide (thereby turning the red color to brown).

After agglutination in accordance with the methods of the invention, the brown agglutinates are discriminated from the red agglutinates either visually or via automated computerized analysis. See specification at page 22 lines 4-14, and page 31 lines 5-17, Table 6 and Figure 6, wherein it is shown that agglutinated cells of one color (e.g., brown) are distinguishable from unagglutinated cells of another color (e.g., red). Applicants respectfully submit that nothing in Chachowski et al. teaches or suggests use of Applicants' methods of treating a population of reagent red blood cells with a dye in order to alter the color of one reagent cell population with respect to the other, and then using the two reagent cell populations simultaneously in one assay to determine reverse ABO blood group or perform an antibody screen.

Applicants therefore respectfully submit that since nothing in Chachowski et al. teaches or suggests *discrimination of two distinct cell populations in a single test*, the instant claims are patentable thereover and the rejection should be withdrawn.

Claims 16, 20, 22, 23 and 25-28 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ullman (U.S. Pat. No. 4,584,277) in view of Vorpahl et al (U.S. Pat. No. 5,071,774) and Chang et al (U.S. Pat. No. 4,748,129) for reasons of record; the Examiner avers that the teachings of Ullman are as set forth above and differ from the invention as instantly disclosed in not teaching agglutination of the erythrocytes and in not teaching fluorophore incorporated into the erythrocytes. In particular, the Examiner avers that Vorpahl et al. teach that determination of the agglutination of two sets of

red blood cells can be used for determination of the presence of an agglutinating agent for one or both of the red blood cell sets (see e.g. col. 9); that as in Ullman, combined addition of means for separately agglutinating two sets of red blood cells (e.g., anti-blood group antigen antibodies) along with the two sets of erythrocytes (e.g. erythrocytes having blood group antigens thereon), at least one of the sets being labeled with a fluorophore such that the sets are separately detectable and distinguishable, to a sample is used in the method.

The Examiner further avers Chang et al. teach the addition of a fluorescent agent capable of incorporation into a cell as a means of labeling erythrocytes for agglutination assays, and that suitable fluorescent agents are taught (e.g. col. 4-7).

The Examiner avers it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used agglutinating anti-blood group antigen antibodies, as in Vorpahl et al, in the method of Ullman because one would have expected such antibodies to perform their expected and desired binding function in the assay of Ullman, as modified, and would not have expected such agglutinating antibodies to interfere in the determination because Vorpahl et al. teach that agglutination is desirable and detectable with a method of like design; that it would have been further obvious to have used a fluorescent agent capable of incorporation into a cell, as in Chang et al., as the means of labeling erythrocytes in Ullman because Ullman requires fluorescently labeled erythrocytes, Chang et al teach incorporated labeling as particularly useful in

assays typing red blood cells, and one would have expected the incorporated labeling to function as desired for providing fluorescently labeled cells in Ullman, as modified. The use of any known and available fluorescent agent capable of incorporation into a cell having the properties preferred by Chang et al would have been an obvious substitution to one of ordinary skill in the art. It would have been further obvious, the Examiner avers, to formulate the reagents of Ullman, as modified, into a kit since that is conventional for convenience, economy, and reproducibility. In addition, the Examiner notes that the recitation of column agglutination technology for visual analysis is in the alternative.

Applicants respectfully submit that in view of the claim amendments and the fact that all claims, both amended and newly presented, require visual or automated computerized analysis of agglutinates, nothing in Ullman when combined with Vorpahl and Chang render these claims unpatentable, as each of Ullman, Vorpahl and Chang are directed to labeling of cells with fluorochromes, and detecting result using fluorescent spectroscopy. In further contrast, Applicants' claimed methods are directed to detection of two populations using reagent red blood cells, one population of which are stained. After agglutination in accordance with the methods of the invention, the agglutinates of one color are discriminated from the unagglutinated cells of the other color either visually or via automated computerized analysis as disclosed in the specification. See specification at page 22 lines 4-14, and page 31 lines 5-17, Table 6 and Figure 6, wherein it is shown that agglutinated cells of one color (e.g., brown) are

distinguishable from unagglutinated cells of another color (e.g., red).

Applicants therefore respectfully submit that since nothing in Ullman when combined with Vorpahl et al. and Chang et al. teach or suggest the *discrimination of two distinct cell populations in a single column*, the instant claims are patentable thereover and the rejection should be withdrawn.

Claims 16, 20, 22, 23, and 25-27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chachowski et al (U.S. Pat. No. 5,552,064) in view of Shen et al (U.S. Pat. No. 5,594,808) for reasons of record; the Examiner avers that the teachings of Chachowski et al. are as set forth previously and differ from the invention as instantly claimed in not teaching an apparatus for interpretation of agglutination results; that Shen et al. teach an apparatus and method for classifying agglutination reactions in column agglutination devices; and that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used the device of Shen et al for interpreting the results of Chachowski et al. because of the express suggestion in Shen et al. to do so. The Examiner thus concludes that the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Applicants respectfully submit that nothing in Chachowski et al. either alone or when combined with Shen et al. teach the claimed detection using two cell populations in a single test. Chachowski et al. is directed to use of column agglutination technology (CAT)

to detect presence of binding ligands, for example, blood group antigens or antibodies thereto, using separate forward and reverse or crosscheck tests, further employing a separation matrix. Shen et al. is directed to an automated computerized imaging system that is used to detect optically detectable binding complexes for example, carrier-bound antigens or antibody complexes and non-complexed carrier-bound antibodies and antigens, that form an agglutination pattern in microreaction vessels such as those used for column agglutination technology (CAT).

Nothing in Chachowski et al. or Shen et al. either teaches or suggests, nor would the teachings either alone or when combined motivate one to Applicants' methods of treating a population of reagent red blood cells with dye in order to alter the color of one population with respect to the other. In Applicants' visual and automated computerized analysis methods, Applicants teach treatment of one population of reagent red blood cells with sodium azide or cyanide (thereby turning the red color to brown). After agglutination in accordance with the methods of the invention, the brown agglutinates are discriminated from the red agglutinates either visually or by using an automated computerized imaging technology. See specification at page 22 lines 4-14, and page 31 lines 5-17, Table 6 and Figure 6, wherein it is shown that agglutinated cells of one color (e.g., brown) are distinguishable from unagglutinated cells of another color (e.g., red).

Applicants therefore respectfully submit that since nothing in Chachowski et al. when combined with Shen et al. teaches *discrimination of two distinct cell*

populations in a single test, the instant claims are patentable thereover and the rejection should be withdrawn.

For the above-stated reasons and in light of Applicants' amendments made herein, it is respectfully submitted that the claims are patentable over the art cited. Applicants therefore request that the rejections be withdrawn and the claims be allowed.

Please charge the fees due in connection with the filing of this amendment to Deposit Account No.10-0750/CDS-221/CKG in the name of Johnson & Johnson.

Respectfully submitted,

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EXHIBIT A

16. [Twice Amended] A method of analyzing blood in a reverse test, comprising:

(a) [reacting] admixing a sample of blood with [anti-A and anti-B antibodies;]

[(b) reacting a sample of blood with] reagent red blood cells bearing A antigen and with reagent red blood cells bearing B antigen wherein such admixing is performed in a single test;

(b) allowing the admixture to agglutinate;

(c) subjecting the [sample] admixture to visual or automated computerized imaging [or spectrophotometric] analysis; and

(d) analyzing the visual or automated computerized imaging [or spectrophotometric] analysis to determine ABO reverse type[;

wherein the visual analysis comprises column agglutination technology].

20. [Amended] The method of claim 16 wherein [the] one group of reagent red blood cells of step ([b]a) are stained.

22. [Twice Amended] The method of claim [20] 29 wherein the column agglutination technology is a column agglutination test reaction and separation vessel in cassette form.

25. A method of [performing simultaneous forward and reverse] determining reverse ABO type of two cell populations in a single test, comprising:

(a) [reacting] admixing a sample of blood with [anti-A and anti-B antibodies wherein the antibodies are bound to a detectable label; and]

[(b) reacting a sample of blood with] reagent red blood cells bearing [labeled] A antigen and

reagent blood cells bearing [labeled] B antigen, wherein such admixing is performed in a single test;

(b) allowing the admixture to agglutinate;

(c) subjecting the [sample] admixture to visual or automated computerized imaging [or spectrophotometric] analysis; and

(d) analyzing the visual or automated computerized imaging [or spectrophotometric] analysis to determine reverse ABO type[;

wherein the visual analysis comprises column agglutination technology].

26. The method of claim 25 wherein [the] one group of reagent red blood cells of step ([b]a) are stained.

27. The method of claim [26] 30 wherein the column agglutination technology is a column agglutination test reaction and separation vessel in cassette form.

--29. [New] The method of claim 20 wherein the single test subjected to visual or automated computerized imaging analysis is selected from the group consisting of tube, microplate, slide, slide platform and column agglutination technology.

30. [New] The method of claim 25 wherein the single test subjected to visual or automated computerized imaging analysis is selected from the group consisting of tube, microplate, slide, slide platform and column agglutination technology.

31. [New] A method of simultaneous blood antibody testing of two cell populations, comprising:

(a) admixing a sample of blood with a first group of reagent red blood cells bearing a first antigen and a second group of reagent red blood cells bearing a second antigen, wherein such admixing is performed in a single test;

(b) allowing the admixture to agglutinate;

(c) subjecting the admixture to visual or automated computerized imaging analysis; and

(d) analyzing the visual or automated computerized imaging analysis to determine reverse ABO type.

32. [New] The method of claim 31 wherein one group of reagent red blood cells of step (a) are stained.

33. [New] The method of claim 32 wherein the single test subjected to visual or automated computerized imaging analysis is selected from the group consisting of tube, microplate, slide, slide platform and column agglutination technology.

34. [New] The method of claim 33 wherein the column agglutination technology is a column agglutination test reaction and separation vessel in cassette form.

35. [New] The method of Claim 34 wherein an automated computerized imaging system is employed to interpret an agglutination result.

36. [New] A method of performing an antibody screen in a single test comprising:

(a) admixing a sample of blood with reagent red blood cells bearing a first antigen and reagent red blood cells bearing a second antigen, wherein one of the populations of red blood cells is stained;

(b) allowing the admixture to agglutinate;

(c) subjecting the admixture to visual or automated computerized imaging analysis; and

(d) detecting and identifying the antibody.

37. [New] The method of claim 36 wherein the sample of blood is serum or plasma.

38. [New] The method of claim 37 wherein one group of reagent red blood cells of step (a) are stained.

39. [New] The method of claim 38 wherein the single test subjected to visual or automated computerized imaging analysis is selected from the group consisting of tube, microplate, slide, slide platform and column agglutination technology.

40. [New] The method of claim 39 wherein the column agglutination technology is a column agglutination test reaction and separation vessel in cassette form.

41. [New] The method of Claim 40 wherein an automated computerized imaging system is employed to interpret an agglutination result.

42. [New] A blood analysis kit for performing an antibody test comprising:

(a) a container having therein reagent red blood cells bearing a first antigen and reagent red blood cells bearing a second antigen, wherein one of the populations of reagent red blood cells is stained;

(b) reaction means for carrying out the antibody test; and

(c) instructions for performing the antibody test in order to detect and identify the antibody.

43. [New] The kit of claim 42 wherein the reagent red blood cells are selected from the group consisting of groups A1, A2, B, O, D, C, E, c, e, M, N, S, s, P_1, Le^a, Le^b, K, k, Js^a, Fy^a, Fy^b, Jk^a, Jk^b, Lu^a, and Lu^b.

44. [New] The kit of claim 42 wherein the reaction means for carrying out the antibody test is selected from the group consisting of tube, microplate, slide, slide platform and column agglutination technology.

45. [New] The kit of claim 44 wherein the reaction means for carrying out the antibody test is a column agglutination test reaction vessel.

46. [New] A blood analysis kit for performing a reverse ABO blood type comprising:

(a) a container having therein reagent red blood cells bearing group A antigen and reagent red blood cells bearing B antigen, wherein one of the populations of reagent red blood cells is stained;

(b) reaction means for carrying out the reverse ABO blood type; and

(c) instructions for performing the reverse ABO blood type.

47. [New] The kit of claim 46 wherein the reaction means for performing the reverse ABO blood type is selected from the group consisting of tube, microplate, slide, slide platform and column agglutination technology.

48. [New] The kit of claim 47 wherein the reaction means for carrying out the reverse ABO blood type is a column agglutination test reaction vessel.

49. [New] The method of claim 16 wherein the sample of blood is serum or plasma.

50. [New] The method of claim 25 wherein the sample of blood is serum or plasma.

51. [New] The method of claim 31 wherein the sample of blood is serum or plasma.--